



**21st International Ultmann Chicago Lymphoma Symposium**

# **Phosphatidylinositol 3-Kinase (PI3K): Is Targeting This Pathway Still Valuable?**

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**Director and Associate Professor**

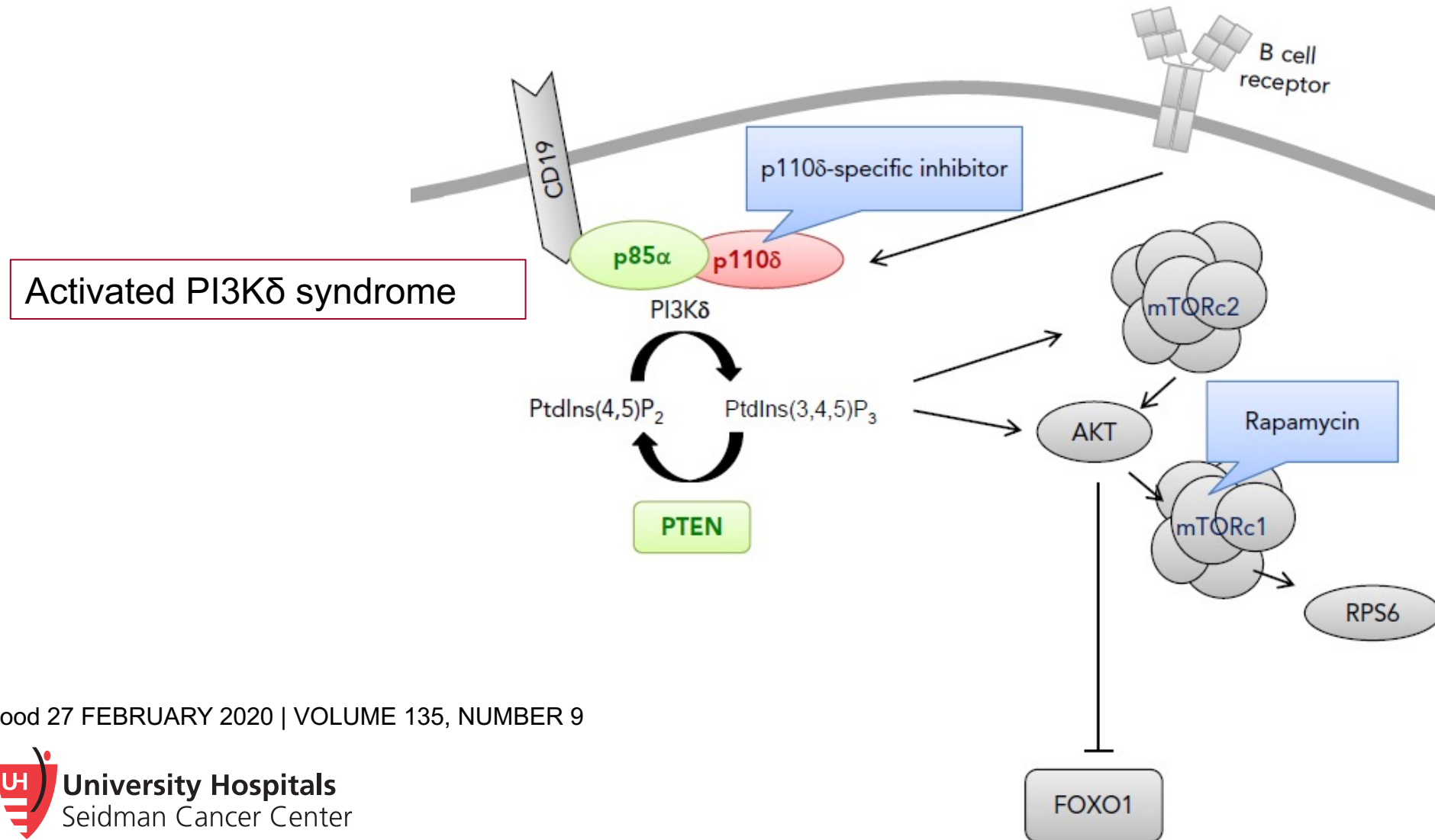
**University Hospitals Seidman Cancer Center, and  
Case Western Reserve University**

# Outline

- **Approval history of PI3K inhibitors in lymphoma and CLL**
- **Safety concerns**
- **Opportunities**

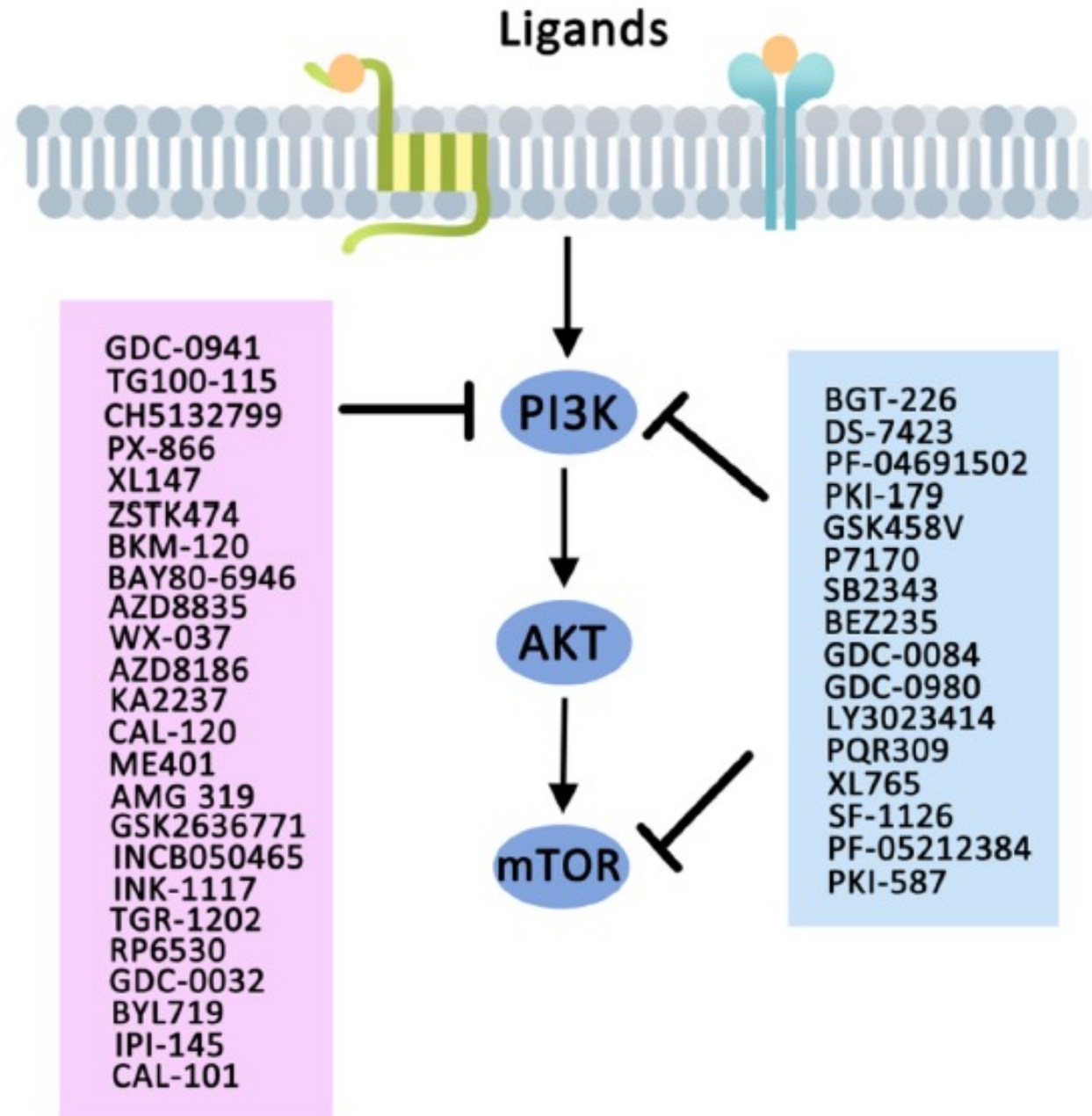
# Increased activation of PI3 kinase- $\delta$ predisposes to B-cell lymphoma

Anne Durandy and Sven Kracker



Blood 27 FEBRUARY 2020 | VOLUME 135, NUMBER 9

# Once upon a time, many PI3K Inhibitors...

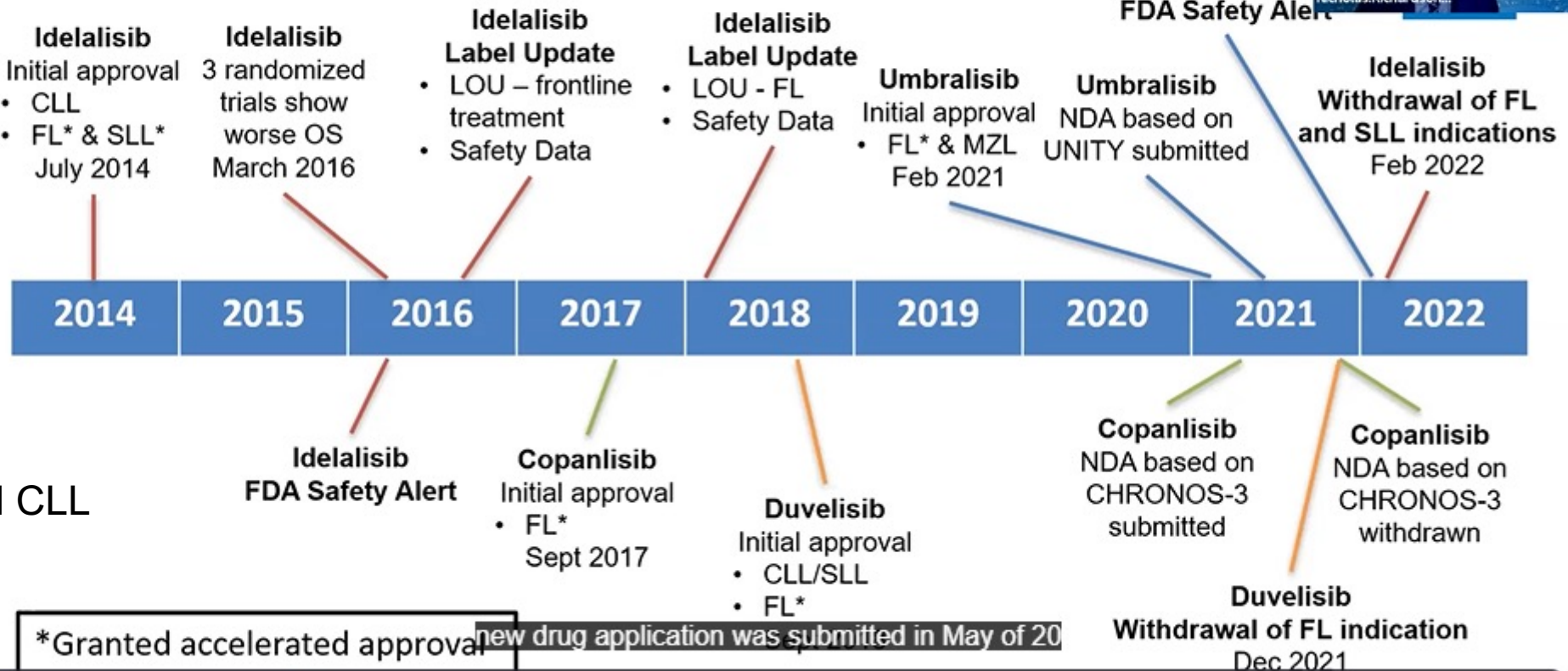


Yang et al. Molecular Cancer (2019)

# Today, “The Saga of PI3K Inhibitors” Suffers Regulatory Withdrawals

Nicholas Richardson (FDA)

## Regulatory History - Approved PI3K Inhibitors



Idelalisib: relapsed CLL  
Duvelisib: RR CLL

## PI3K Inhibitors Impart Substantial Risk



	Idelalisib N = 146	Copanlisib N = 244	Duvelisib N = 442	Umbralisib N = 371
Grade ≥3 adverse event	71%	85%	84%	51%
Serious adverse event	50%	51%	65%	26%
Grade ≥3 Infection	23%	23%	27%	20%
Grade ≥3 Neutropenia*	28%	29%	43%	17%
Grade ≥3 Diarrhea-Colitis	14%	5%	23%	7%
Grade ≥3 ALT/AST increase*	18%	2%	8%	7%
Grade ≥3 Rash	4%	2%	9%	3%
Any Grade Pneumonitis	5%	7%	7%	1%
Grade ≥3 Hyperglycemia*	-	34%	-	-
Grade ≥3 Hypertension	-	29%	-	-

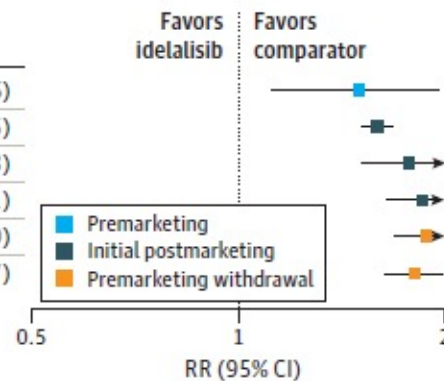
as monotherapy. The incidence of the respective grade

Fatal AEs, possible increased risk of death... (Idelalisib, Duvelisib, Umbralisib)

**A** Serious adverse events

## Serious adverse events

Year	Sales in millions, \$	Trial	Total participants	RR (95% CI)
2013	0	NCT01539512	220	1.48 (1.12-2.96)
2016	323	NCT01980888	531	1.58 (1.34-1.86)
NA	323	NCT01732926	817	1.77 (1.51-2.08)
NA	323	NCT01732913	1292	1.86 (1.63-2.11)
2018	605	NCT01659021	1553	1.87 (1.67-2.10)
2019	708	NCT01569295	1969	1.79 (1.63-1.97)

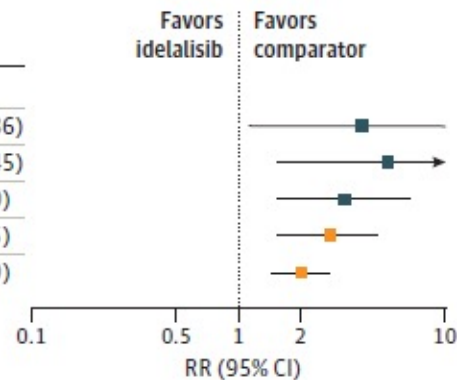


...serious risks of SAE, FAE, and death with idelalisib treatment were evident by 2016.

**B** Fatal adverse events

## Fatal adverse events

Year	Sales in millions, \$	Trial	Total participants	RR (95% CI)
2013	0	NCT01539512	220	
2016	323	NCT01980888	531	3.96 (1.13-13.86)
NA	323	NCT01732926	817	5.23 (1.57-17.45)
NA	323	NCT01732913	1292	3.30 (1.56-7.00)
2018	605	NCT01659021	1553	2.80 (1.58-4.95)
2019	708	NCT01569295	1969	2.05 (1.36-3.09)

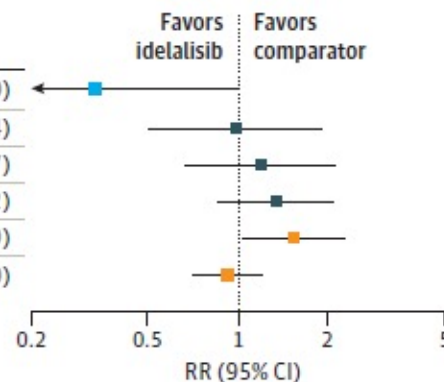


However, idelalisib remained on the market for another 6 years, with minimal evidence generation.

**C** Death

## Death

Year	Sales in millions, \$	Trial	Total participants	RR (95% CI)
2013	0	NCT01539512	220	0.33 (0.11-1.00)
2016	323	NCT01980888	531	0.99 (0.51-1.94)
NA	323	NCT01732926	817	1.20 (0.66-2.17)
NA	323	NCT01732913	1292	1.35 (0.85-2.12)
2018	605	NCT01659021	1553	1.54 (1.03-2.29)
2019	708	NCT01569295	1969	0.93 (0.72-1.20)



Banerjee, et al. JAMA IM 2023

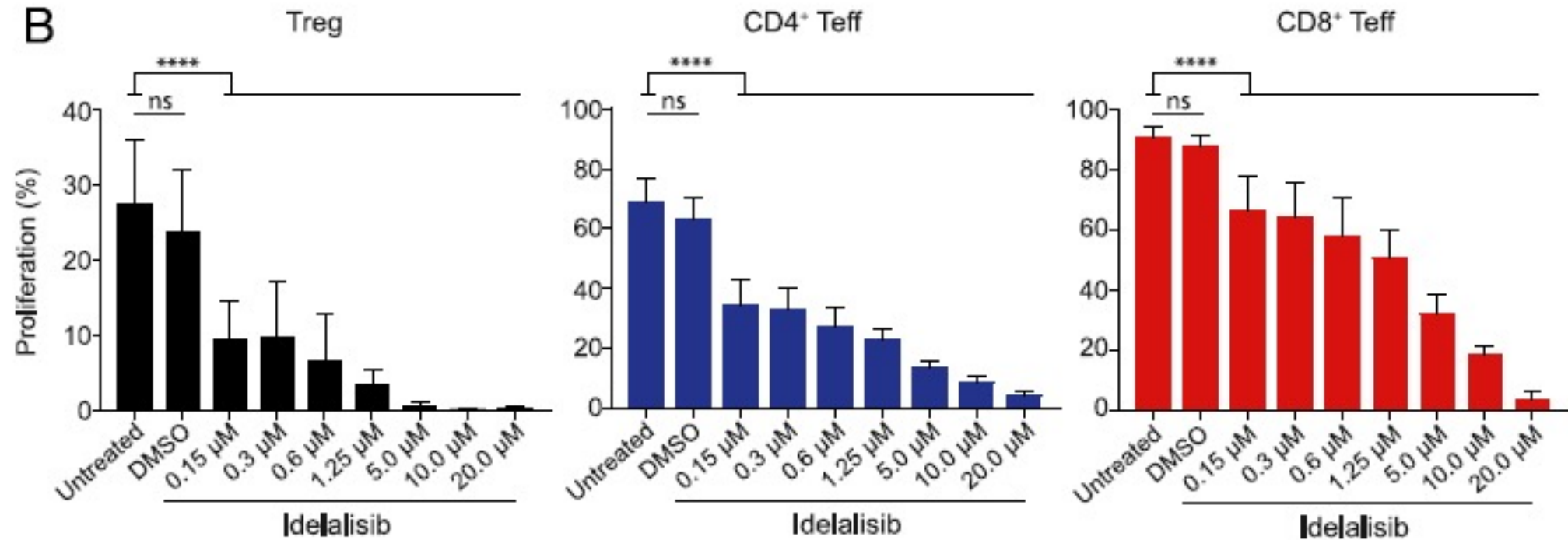
# All toxicities of PI3K inhibitors are not the same

## PI3K $\delta/\alpha$ inhibitor copanlisib demonstrates manageable safety risks

- In R/R B-NHL patients receiving copanlisib monotherapy and combination therapy with rituximab, the risk of any grade AEs was 99% and 96%, respectively, and the risk of grade  $\geq 3$  AEs was 84% and 91%, respectively.
- The common grade  $\geq 3$  AEs included hyperglycemia (45.14%), hypertension (35.07%), neutropenia (14.75%), pneumonia (7.03%), and diarrhea (5.09%).
- “Compared to the serious toxicities caused by idelalisib and duvelisib (21), copanlisib seems to have manageable safety.”
- The pooled CR, PR, **ORR**, SDR, **DCR**, and PDR from all 8 articles were 13%, 40%, **57%**, 19%, **86%**, and 9%, respectively.

(A meta-analysis of prospective clinical trials. Wang. Frontiers in Immunology. 2022)

# More Worrisome SAEs such as colitis may be due to inhibition of Treg: PI3K p110 $\delta$ Isoform Inhibitor Idelalisib Preferentially Inhibits Human Regulatory T Cell Function



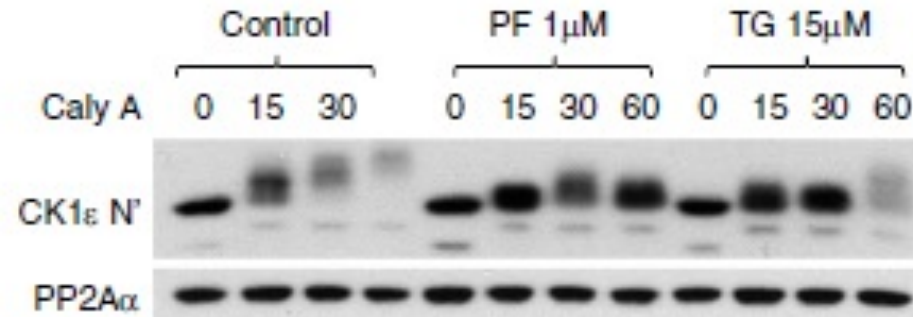
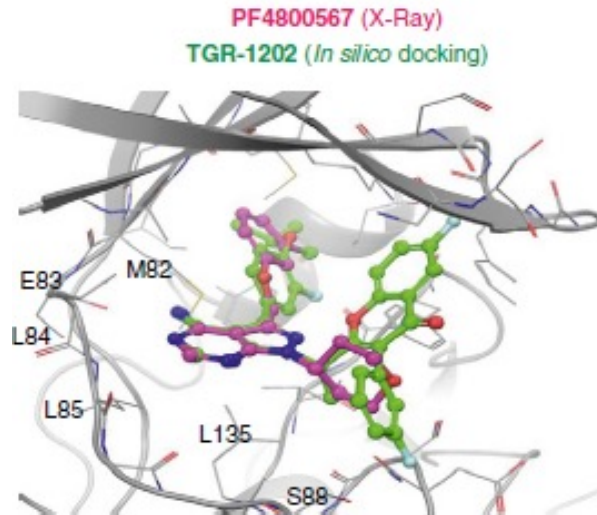
# Umbralisib have a unique profile, and possibly fewer SAEs

## PI3K Inhibitors Impart Substantial Risk

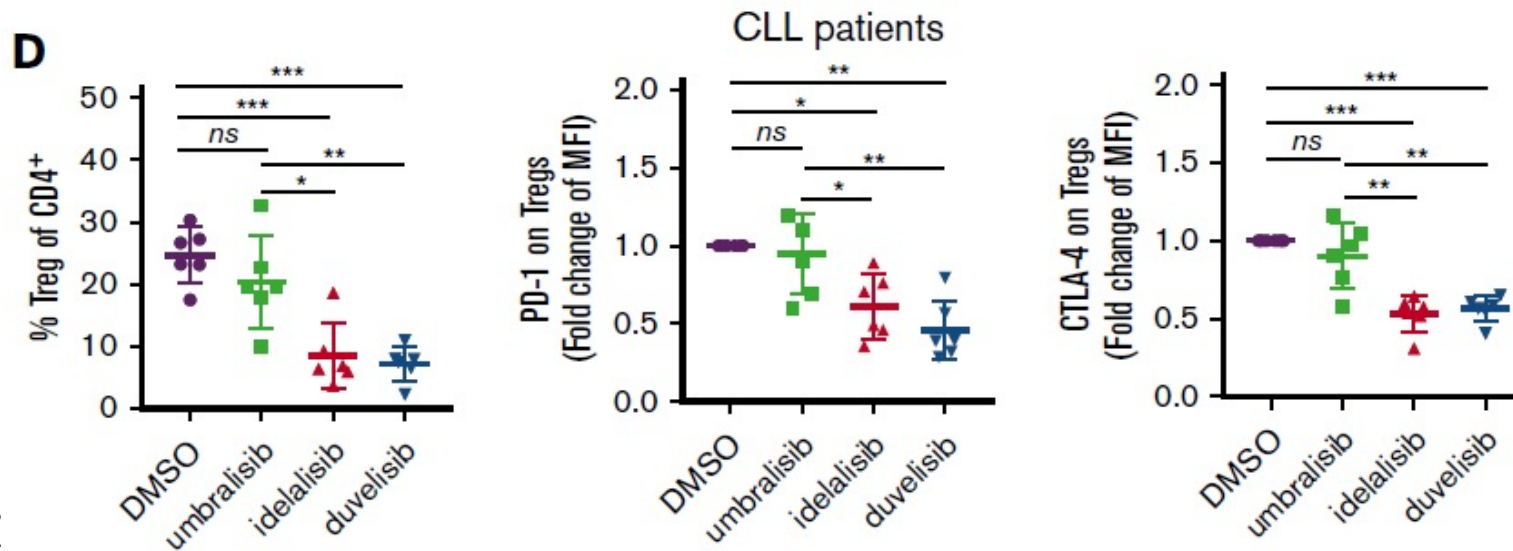
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as monotherapy. The incidence of the respective grade

# Umbralisib is a dual inhibitor of PI3K $\delta$ and CK1 $\epsilon$ , and is associated with differential effects on Treg and animal models of intestinal injury

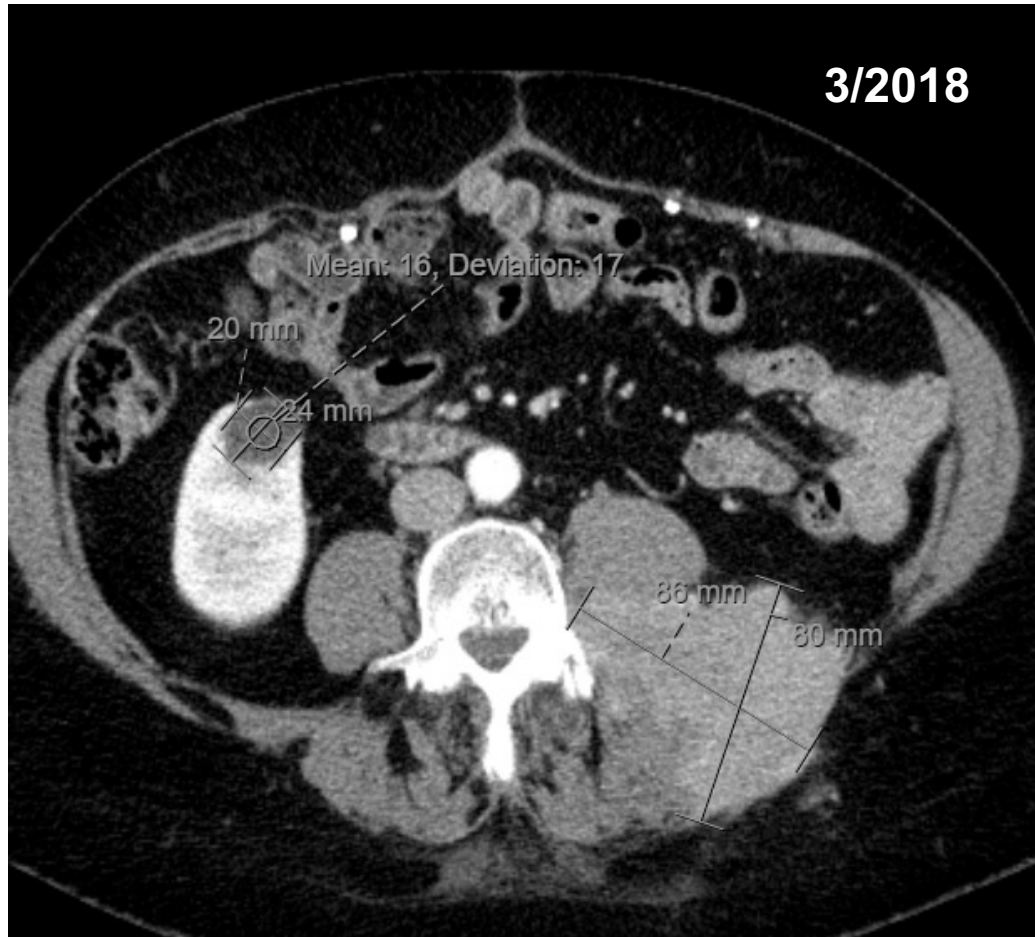


Deng. Blood 2017



Maharaj. Blood Adv 2020

# PI3K Inhibition: curable potential in a RR DLBCL



DLBCL (Tx: include R-CHOP, R-DHAP x2, R-GDP, BEAM-ASCT, protocol of Aurora kinase inhibitor, **umbralisib single agent**)

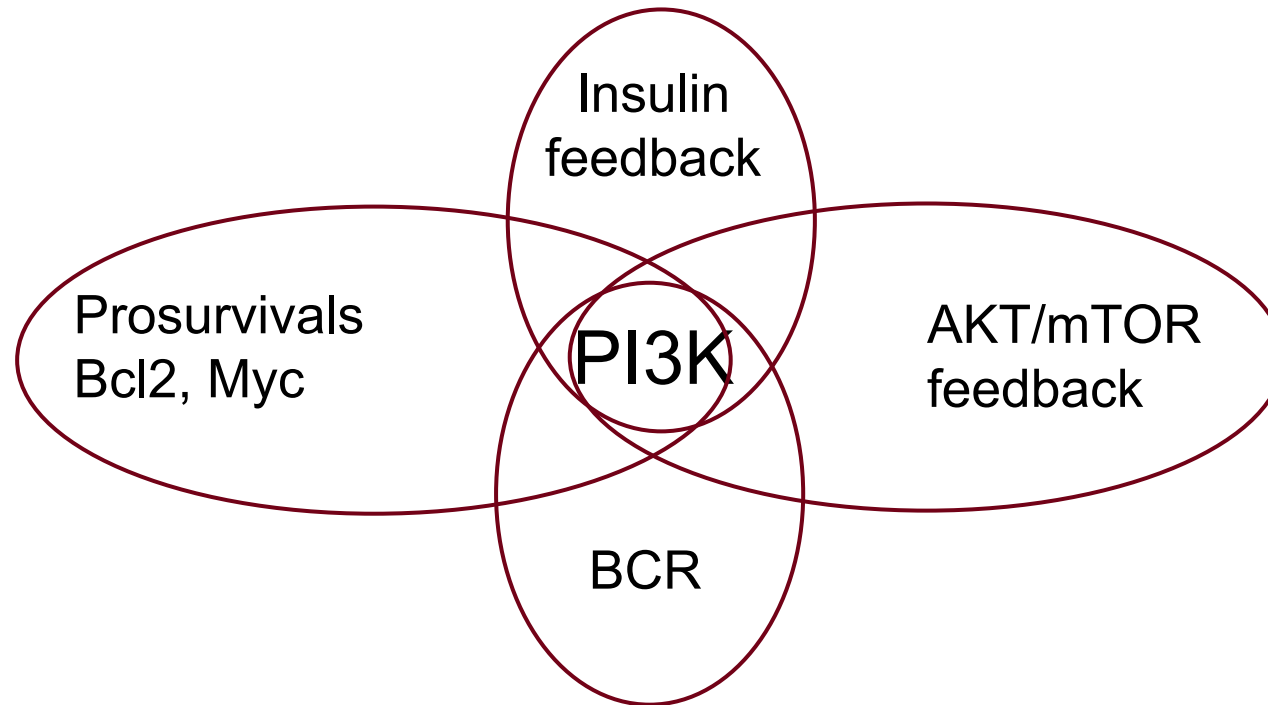
# CLL: opportunities

- Preliminary efficacy in relapses post-BTKi
  - Real world data from the registry of the German CLL Study Group. Tresckow, Annals of Hematology. 2023
  - A Swedish nation-wide real-world report. Mattsson, Eur J Haematol. 2023
- Idelalisib and Duvelisib demonstrated activity in CLL with 17p deletion or TP53 mutation
  - Zelenetz, Lancet onc 2017; Špaček, BJH 2023; Flinn, Blood 2018; O'Brien AM J Hematol 2018
- Investigator initiated trials may provide new insights into exposure, schedule, biomarker, safety, and efficacy.
- New approaches to manage toxicities may mitigate safety risks.

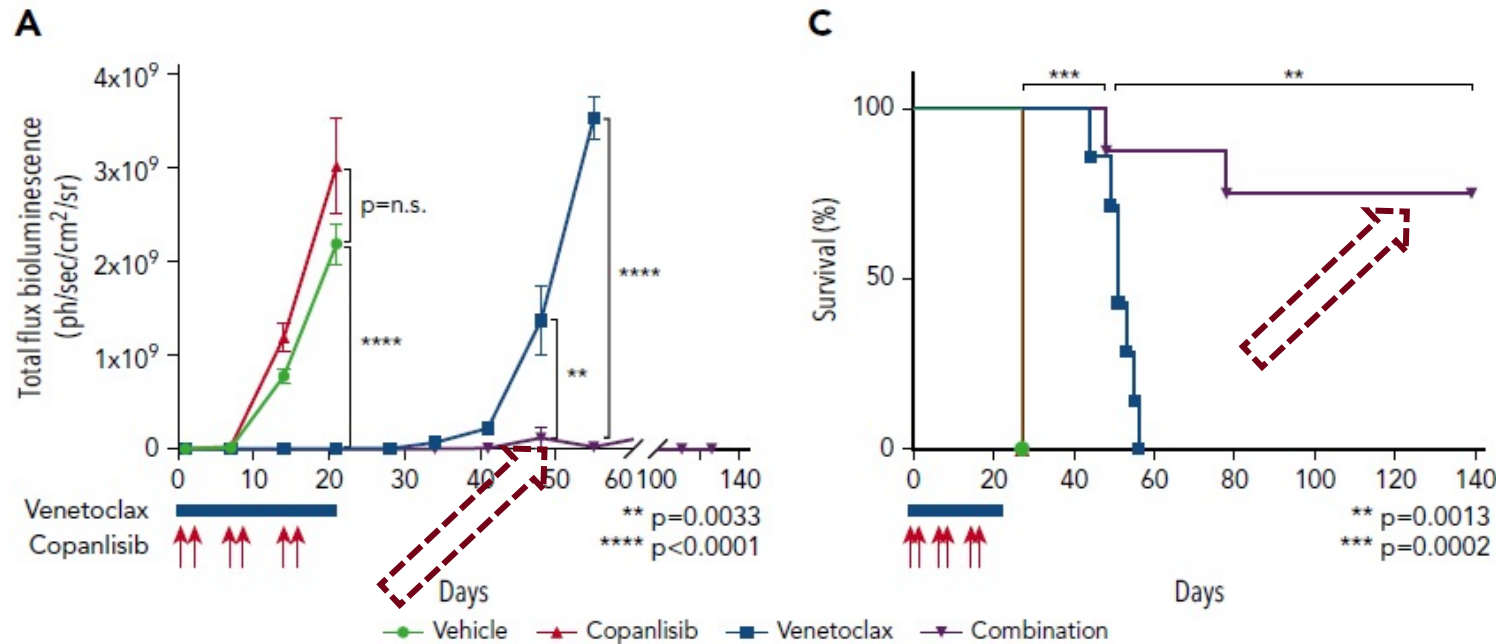
# DLBCL: opportunities

- Many patients remain incurable and need new treatments (e.g. Relapses after CAR-T).
- Emerging data suggest opportunities to integrate or enhance PI3K inhibition and tumor control.

Combination  
strategies



# PI3K $\alpha/\delta$ blockage + BCL-2 inhibition highly effective in DLBCL mouse models



## A Phase I Study of Copanlisib and Venetoclax in Patients with RR DLBCL

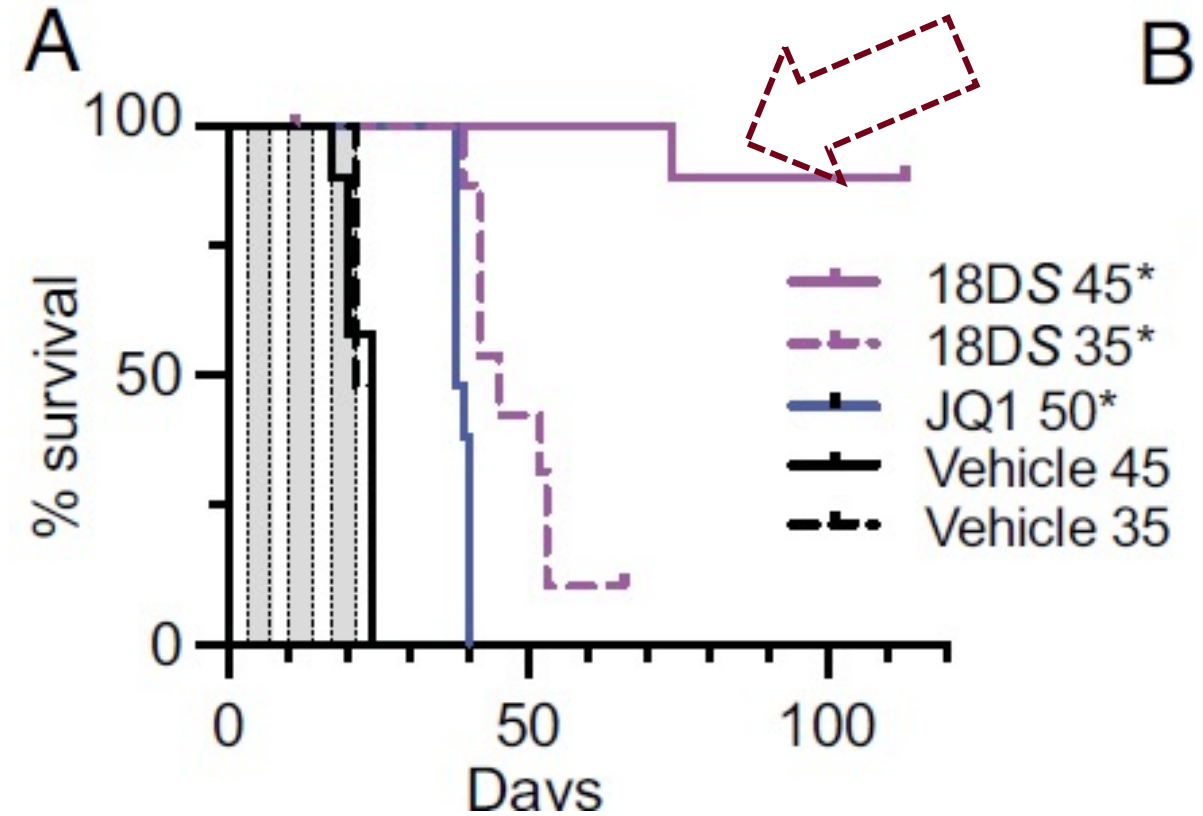
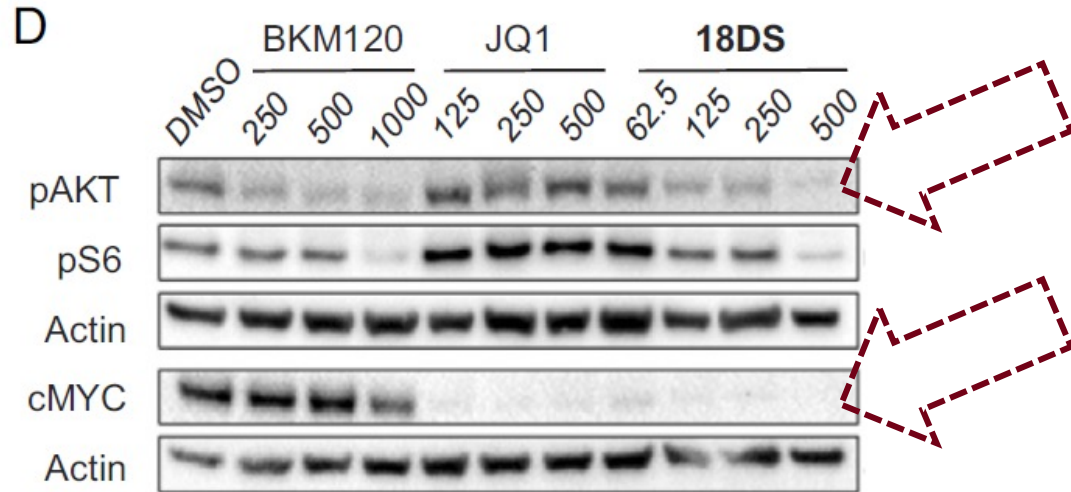
- As of July 21, 2023, 12 pts were evaluable. Patients were treated in DL +1 (n=5), DL +2 (n=3), and DL +3 (n=4).
- No DLTs observed.
- 1 pt in DL +1, who had received >5 lines of prior therapy, achieved a CMR, with response lasting 3 months.

## BCR-dependent DLBCLs with genetic bases for BCL-2 dysregulation

(Bojarczuk, et al. Blood 2019)

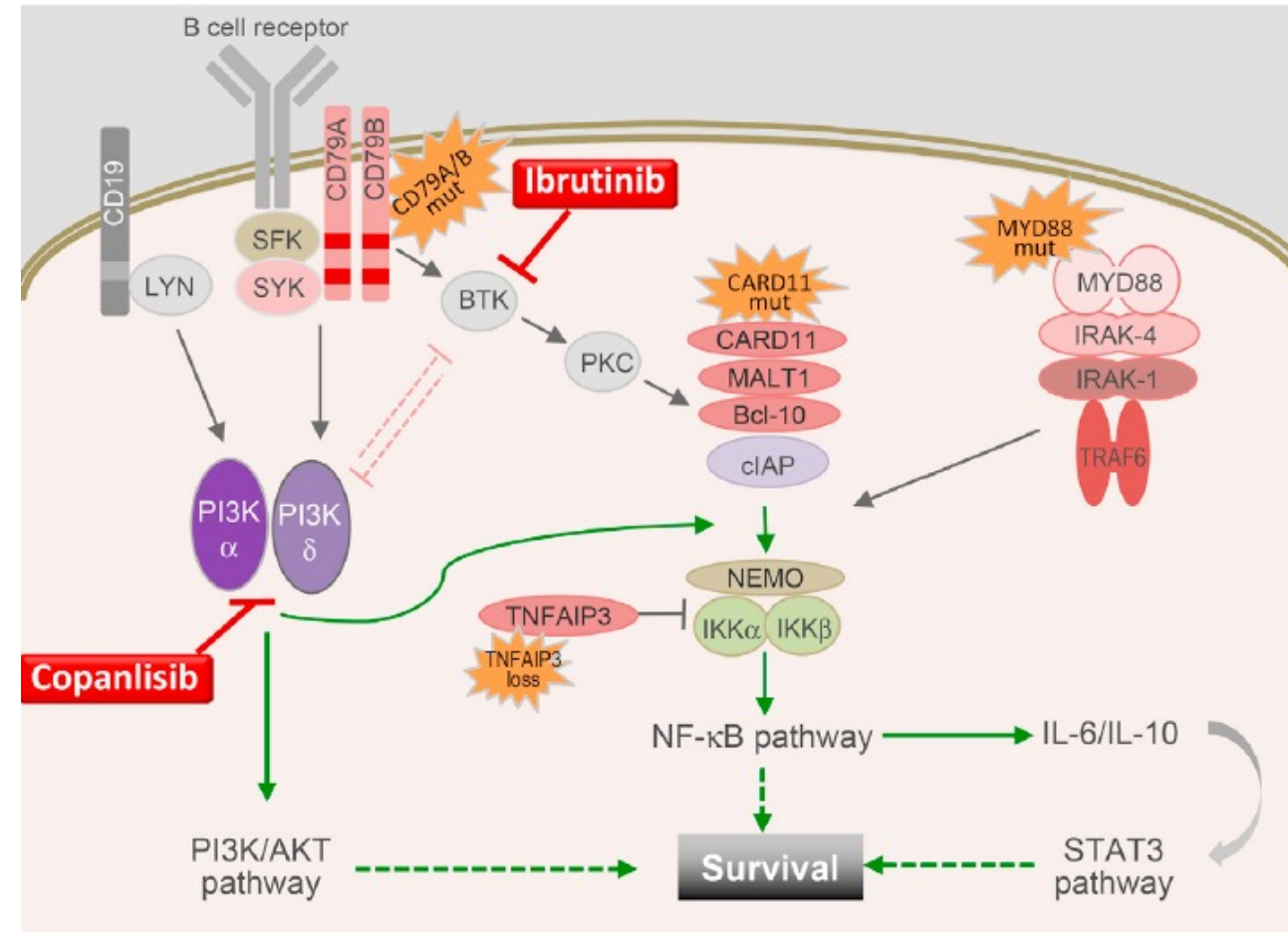
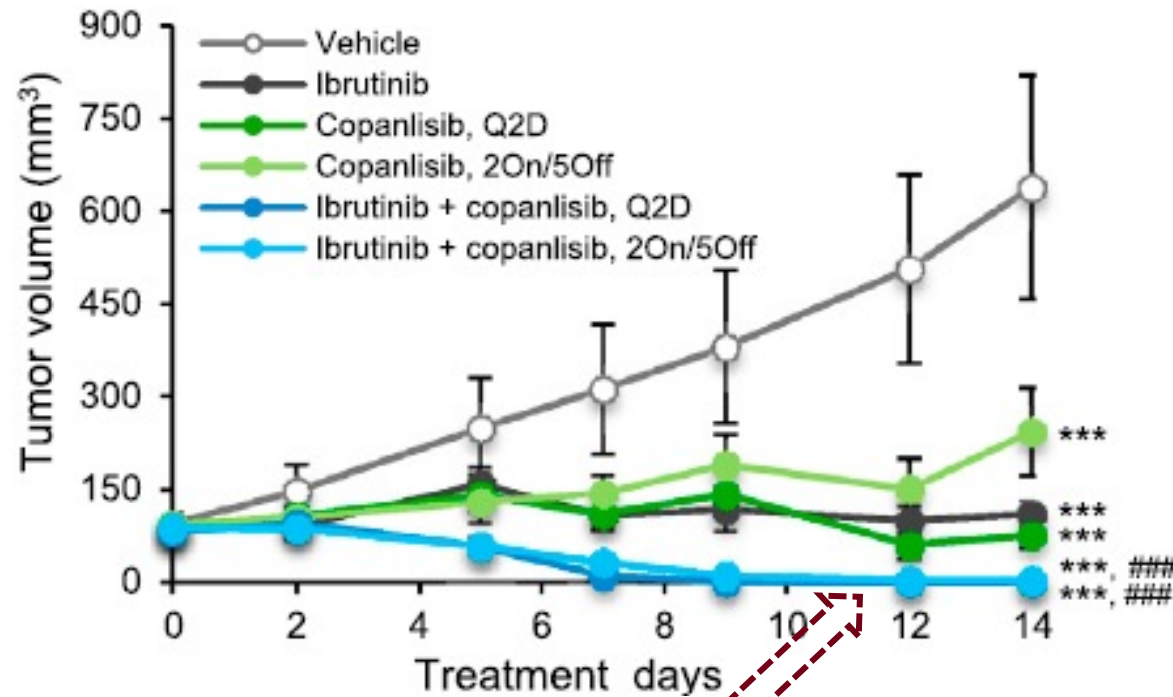
(Crombie et al. ASH abstract 2023)

# PI3K $\alpha/\delta$ blockage + bromodomain inhibition highly effective in DLBCL mouse models



# Simultaneous Inhibition of PI3K $\delta$ and PI3K $\alpha$ Induces ABC-DLBCL Regression by Blocking BCR-Dependent and Independent Activation of NF- $\kappa$ B and AKT

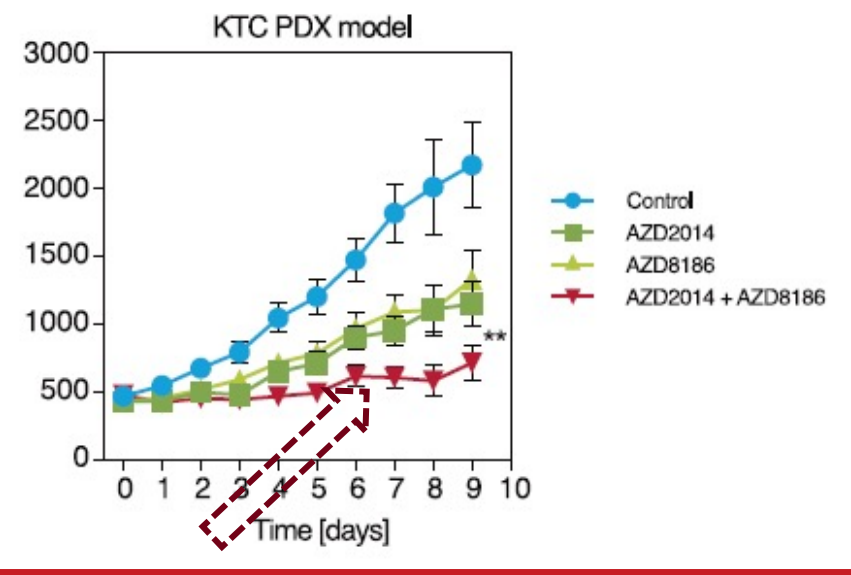
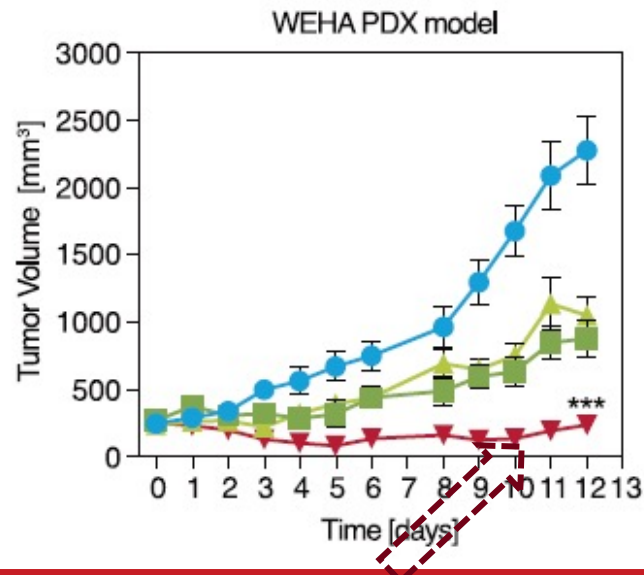
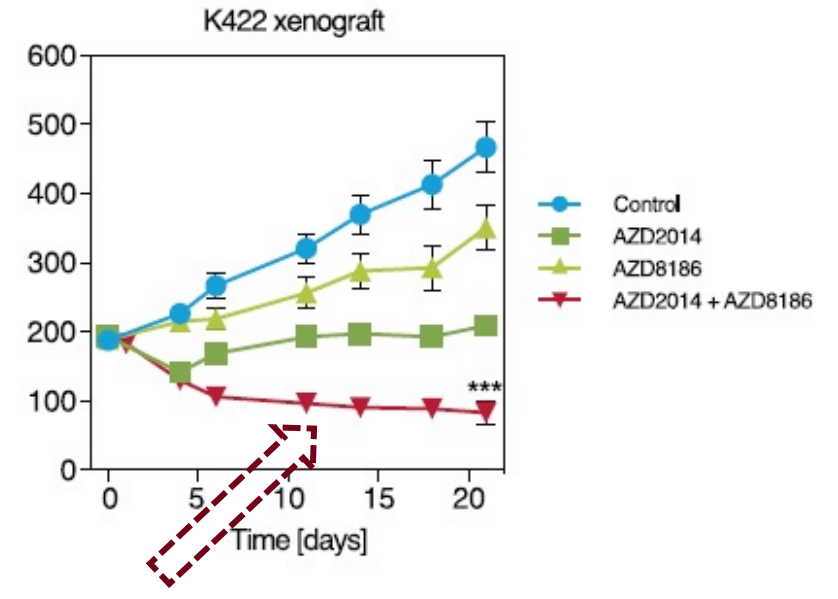
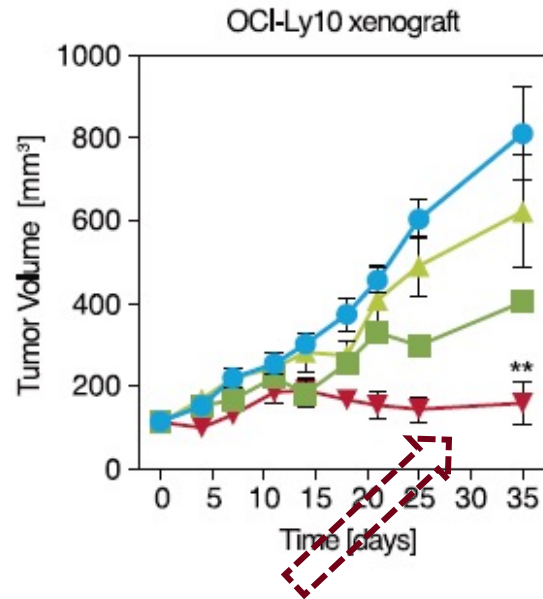
Paul et al. Cancer Cell 2018



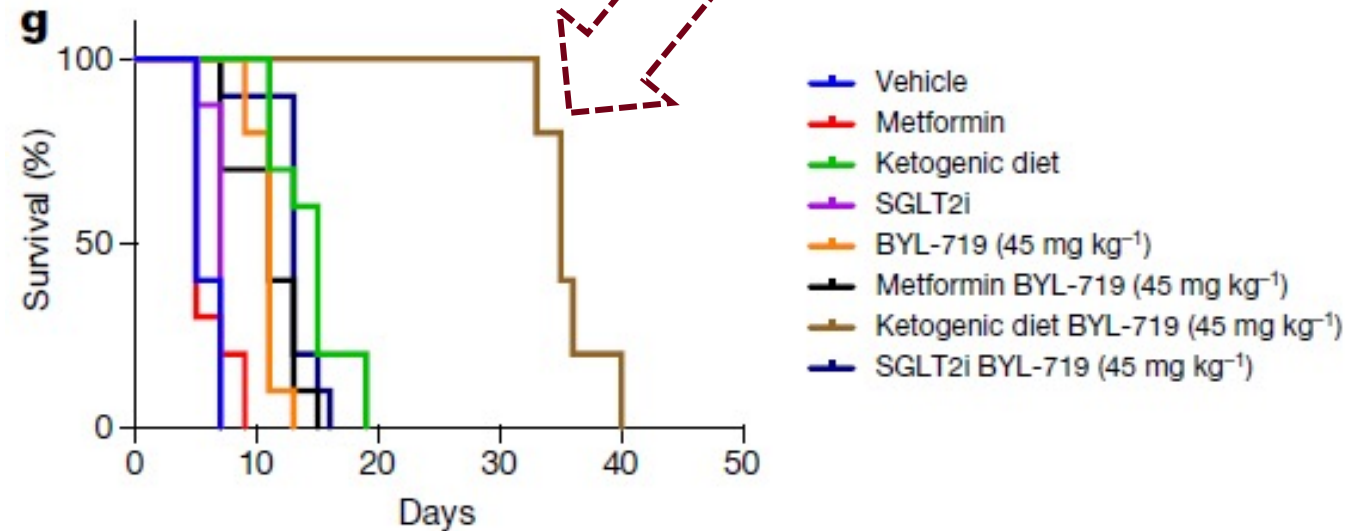
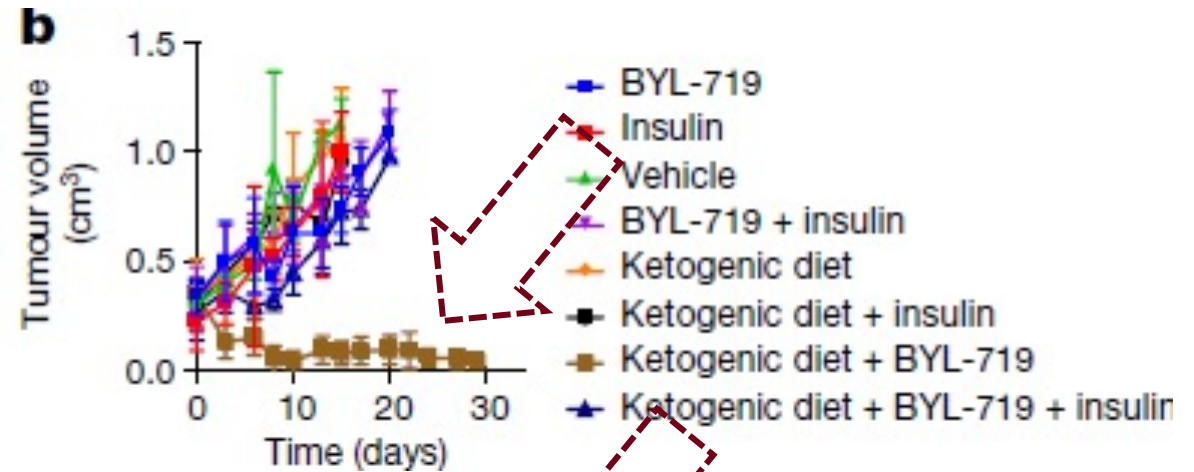
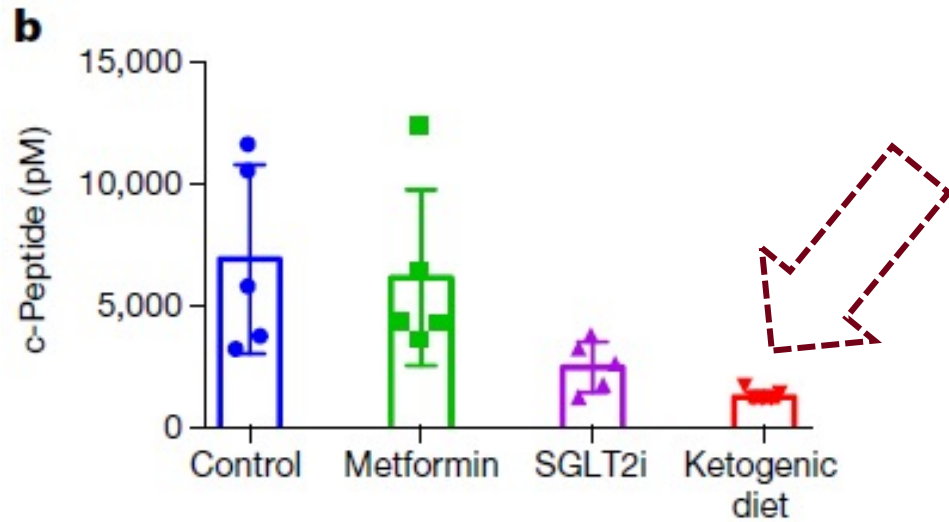
# PI3K $\beta/\delta$ blockage + mTOR inhibition effective in animal models of aggressive lymphoma

- PI3K $\beta/\delta$  blockage using AZD8186 may be limited by feedback activation of the PI3K/AKT/mTOR pathway.
- AZD8186 plus the mTOR inhibitor AZD2014 overcame resistance to PI3K $\beta/\delta$  inhibition.

Xu et al. Leukemia 2023



# Suppression of insulin feedback enhances the efficacy of PI3K inhibitors



Hopkins Nature 2018

Christopher Ronald Funk,<sup>1,\*</sup> Shuhua Wang,<sup>1,\*</sup> Kevin Z. Chen,<sup>1</sup> Alexandra Waller,<sup>1</sup> Aditi Sharma,<sup>1</sup> Claudia L. Edgar,<sup>1</sup> Vikas A. Gupta,<sup>1</sup>

**A** CD28/CD19 CART

fusion

Days

OSU-CLL (CD20+CD5+)  
frequency of peripheral  
nucleated cells

Days (post CLL)

Legend:  
 - No CART - CLL only  
 - Control CART cells  
 - Duv CART cells

**B** 4-1BB/CD19 CART

OSU-CLL (CD20+CD5+)  
frequency of peripheral  
nucleated cells

Days (post CLL)

**C** CD28/CD19 CART

Percent survival OSU-CLL  
bearing NOG mice

CART T infusion

Days

**D** 4-1BB/CD19 CART

OSU-CLL (CD20+)  
frequency of peripheral  
nucleated cells

Days



**University Hospitals**  
Seidman Cancer Center

# Targeting PI3K Is Still Valuable in B Cell Neoplasms

- There is compelling evidence that PI3K contributes to tumor growth in CLL and lymphomas, involving intricate interaction with other tumor-promoting pathways and the tumor microenvironment.
- Highly selective PI3K delta inhibitors may be useful in select CLL patients: e.g. relapses after BTKi and BCL2i, bridging therapy.
  - Prolonged treatment may not be feasible or safe.
  - Managing SAEs (infections, colitis) will be critical.
- PI3K inhibition may be combined with other targeting agents in molecularly defined DLBCL.
- Targeting PI3K remains highly valuable, and requires innovative approaches.
  - May be important to avoid unbalanced inhibition of PI3K delta.
  - New chemical entities may be needed.

# Thank you!!

